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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,069	02/13/2002	Charles Andrianjara	A0000434-01-CFP	7470

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WARNER-LAMBERT COMPANY
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EXAMINER

MCKENZIE, THOMAS C

ART UNIT PAPER NUMBER

1624

DATE MAILED: 10/09/2003

11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/075,069

Applicant(s)

ANDRIANJARA ET AL.

Examiner

Thomas McKenzie, Ph.D.

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 August 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-35 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-35 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7&10.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

1. This action is in response to an election and amendments filed on 8/6/03. There are thirty-five claims pending and thirty-five under consideration. Claims 1-32 are compound claims. Claims 33-35 are composition claims. This is the first action on the merits. The application concerns some pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione compounds, compositions, and uses thereof.

Election/Restrictions

2. Applicant's election without traverse of Group X in Paper No. 9 is acknowledged.

Title

3. The title of the invention is no longer descriptive after restriction. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: adding the word "Pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione" to the beginning of the title.

Specification

4. The specification needs to be amended. According to MPEP 201.11, when a non-provisional application is entitled to an earlier U.S. effective filing date of one or more provisional applications under 35 USC 119(e), a statement such as, "This application claims the benefit of U.S. Provisional Application No. 60/-----, filed -- ----." should appear as the first sentence of the specification.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The limitation "substituted 2,4-dioxo-pyrido[3,4-d]pyrimidine" is indefinite. Substituted by what? There is a list of substituents for a generic formula (I) on pages 131-136, are these intended?

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as reasonably to convey to the skilled organic chemist, at the time the application was filed, had possession of the claimed invention. What are the structures and chemical formulas of these claimed substituted 2,4-dioxo-pyrido[3,4-d]pyrimidine compounds and compositions? Applicants define the structures of their claimed compounds by the chemical properties "hydrogen bond acceptor" and "hydrophobic group" along with some geometric parameters. While functional language is permitted in chemical patents, according to the MPEP §2162, "The claimed invention as a

whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function." In the present case Applicants have not even provided a method of making these claimed compounds. According to the MPEP § 2163 I,

"An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S. Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). "Compliance with the written description requirement is essentially a fact-based inquiry that will necessarily vary depending on the nature of the invention claimed. '" I, 296 F.3d at 1324, 63 USPQ2d at 1613."

What are the chemical formulas of the claimed compounds?

Further quoting from the MPEP § 2163 I "A question as to whether a specification provides an adequate written description may arise in the context of an original claim which is not described sufficiently (see, e.g., *Enzo Biochem*, 296

F.3d at 1329, 63 USPQ2d at 1616 (Fed. Cir. 2002); *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398)". "However, as discussed in paragraph I., *supra*, the issue of a lack of adequate written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention. The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art." The critical feature of the present invention is the substituents to be attached to the core 2,4-dioxo-pyrido[3,4-d]pyrimidine ring. Describing chemical compounds by the Cartesian coordinates and the chemical properties of atoms occupying those coordinate locations is hardly conventional in the art of organic chemistry.

7. Claims 1-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making the compounds of two compounds of Examples 53 and 54, does not reasonably provide enablement for making all substituted 2,4-dioxo-pyrido[3,4-d]pyrimidine compounds with the desired chemical properties. The specification does not enable any person skilled organic synthesis, to make the invention commensurate in scope with these claims. "The

factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims”, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Synthesis of any particular substituted 2,4-dioxo-pyrido[3,4-d]pyrimidine compound would first require an understanding of its structure. Without such an understanding, the synthetic chemist would not be able to even devise a synthesis on paper, let alone, perform the synthesis in the laboratory. This is an infinitely large and impossible degree of experimentation. b) The direction concerning the 2,4-dioxo-pyrido[3,4-d]pyrimidine compounds is found in working Examples 53, 54, 69, and 70, in the passages spanning line 13, page 106 to line 20, page 110 and line 27, page 146 to line 6, page 148. There is no general guidance provided for the synthesis of any other substituted 2,4-dioxo-pyrido[3,4-d]pyrimidine compound. c) There are four working example of synthesis of a substituted 2,4-dioxo-pyrido[3,4-d]pyrimidine as discussed above. d) The nature of the invention is chemical synthesis of the uncommon substituted 2,4-dioxo-pyrido[3,4-

d]pyrimidine ring system, which involves chemical reactions. e) The state of the art is that only limited methods of making such rings are known. These methods are not taught in the specification. The state of the art is that the chemist preparing the claimed compounds must know their structures to plan her synthesis. f) The artisan using Applicants invention to prepare the claimed compounds would be a process chemist or pilot plant operator with a BS degree in chemistry and several years of experience. g) Chemical reactions are well-known to be unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18. h) The breadth of the claims includes all of the millions of substituted 2,4-dioxo-pyrido[3,4-d]pyrimidine compounds as well as the presently unknown list of substituents allowed on the core ring.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

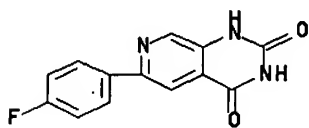
Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

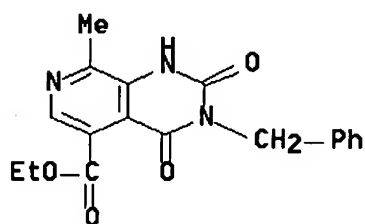
Claims 1-35 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Shen ('679). The compound shown below is a substituted 2,4-dioxo-pyrido[3,4-d]pyrimidine. It has Registry Number 31766-40-2 and the substituent is 6-(p-fluorophenyl). It is found in the reference in the passage spanning line 68, column 22 to line 4, column 23. The authors of this reference are using an especially archaic nomenclature but the basic ring structure is pictured in line 35, column 4. Twelve additional examples are found in lines 5-27, column 23. Lines 30-49, column 3 teach compositions and anti-inflammatory activity of the compounds is taught.



"Recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art. Additionally, where the Patent Office has reason to

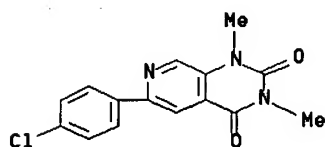
believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on. [58 CCPA at 1031, 439 F.2d at 212-13, 169 USPQ at 229.] This burden was involved in *In re Ludtke*, 58 CCPA 1159, 441 F.2d 660, 169 USPQ 563 (1971), and is applicable to product and process claims reasonably considered as possessing the allegedly inherent characteristics." *In re Swinehart*, 58 CCPA 1027, 439 F.2d 210, 169 USPQ 226 (1971), *In re Best, Bolton, and Shaw*, 195 USPQ 430 (CCPA 1977).

9. Claims 1-32 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kujundzic (Croatia Chemicals). There are seventeen compounds in this reference that anticipate Applicants' claims including the compound shown below. It is a substituted 2,4-dioxo-pyrido[3,4-d]pyrimidine. It has Registry Number 141097-82-7 and the substituents



are 5-carboethoxy, 8-methyl, and 3-(phenylmethyl). It is found in the reference in Scheme II, page 610. It is compound 9, $R = CH_2-C_6H_5$. Synthesis is described in the third paragraph on page 605. Other anticipatory compounds are those of formula 9, Scheme I, page 610 and 4a-4i, Table III, page 603.

10. Claims 1-32 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hirota (Heterocycles). There are four compounds in this reference that anticipate Applicants claims including the compound shown below. It is a substituted 2,4-dioxo-pyrido[3,4-d]pyrimidine.

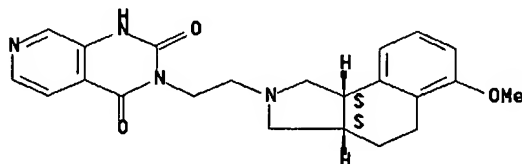


It has Registry Number 154470-82-3 and the substituents are 6-(4-chlorophenyl) and 1,3-dimethyl. It is found in the reference in Scheme 2, page 564. It is compound **4d**. Synthesis is found in the second paragraph, page 568. The other anticipatory compounds are **4a-4c**.

11. Claims 1-35 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Meyer (181). The compound shown below is a substituted 2,4-dioxo-pyrido[3,4-d]pyrimidine. It has Registry Number 179114-55-7 and the substituent is 3-[2-[(3aR,9bR)-1,3,3a,4,5,9b-

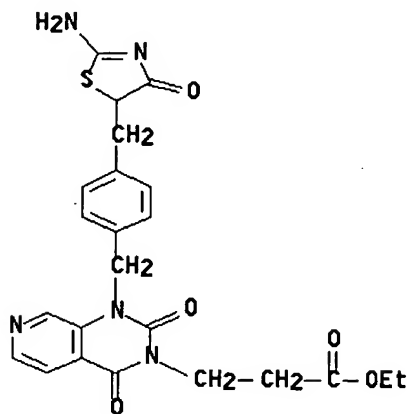
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hexahydro-6-methoxy-2H-benz[e]isoindol-2-yl]ethyl]. It is found in the reference in lines 60, column 41 to line 14, column 42. It is Example 24 and compositions of this substance are found in claim 17 of the reference.



● HCl

12. Claims 1-35 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Sato (JP 8-143568 A2). There are twelve compounds in this reference that anticipate Applicants claims including the compound shown below. It is a substituted 2,4-dioxo-pyrido[3,4-d]pyrimidine. It has Registry Number 180479-11-2 and the substituents are 3-propanoic acid ethyl ester and 1-[[4-[(2-amino-4,5-dihydro-4-oxo-5-thiazolyl)methyl]phenyl]methyl]. It is found in the reference in the passage spanning columns 30 to 31. Applicants attention is drawn to compounds XXXXIV and XXXXV, found in columns 37 to 40 of the reference. These compounds are big and flexible enough to fit any geometric constraint.

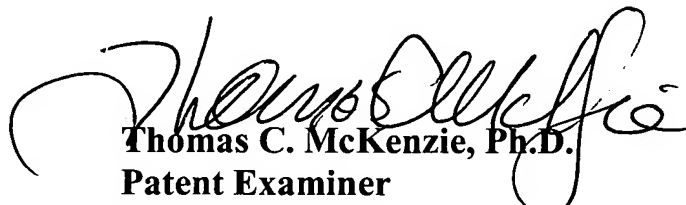


Conclusion

13. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

TCMcK




Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624